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Prednisolone concentrations in cerebrospinal fluid after different prednisolone prodrugs

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The concentration-time curves of prednisolone in cerebrospinal fluid (CSF) and plasma were measured following an equimolar i.v. bolus dose of prednisolone phosphate (five patients) and prednisolone phthalate (four patients). Independent of the prodrug administered, the value of the AUC (0,360 min) in CSF was more than three times lower than the corresponding value in plasma. The AUCs of unbound prednisolone in plasma were higher after prednisolone phosphate, than after prednisolone phthalate (68.1 ± 15.7 *vs* 19.0 ± 5.2 μg ml^{-1} min, $P < 0.001$). Similarly, the AUCs of prednisolone were higher in the CSF after prednisolone phosphate, than after prednisolone phthalate (17.6 ± 2.8 *vs* 3.3 ± 1.0 μg ml^{-1} min, $P < 0.0001$). The results indicate that the concentrations of prednisolone in CSF are much lower than the unbound concentrations in plasma and that therapeutic inequivalence should be expected when the two prodrugs are given in equimolar doses.

Keywords prednisolone prodrug cerebrospinal fluid

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Introduction

The effectiveness of corticosteroids in the treatment of diseases of the central nervous system is subject to debate (Capildeo, 1989; Galicich & French, 1961; Giannotta *et al.*, 1984; Molofsky, 1984). Despite large numbers of trials of corticosteroid therapy in neurological and neurosurgical disorders, little information is available on correlations between the dose and drug concentrations in plasma, central nervous system or CSF. Recently, plasma and CSF concentration-time profiles after an intravenous bolus dose of prednisolone phosphate were measured in three rhesus monkeys by Balis *et al.* (1987). The CSF concentrations of prednisolone were very low and it was suggested that this might be one reason for the poor efficacy of prednisolone in the treatment of central nervous system leukemia in man (Jones *et al.*, 1975, 1984). The purpose of the present study was to investigate the relationship between prednisolone concentrations in plasma and CSF in humans after intravenous administration of equimolar doses of two prednisolone prodrugs, prednisolone phosphate and prednisolone phthalate. These esters were chosen because they exhibit marked differences in their kinetics and in their immunosuppressive effects (Frey *et al.*, 1984, 1985).

Methods

Patients

Nine surgical patients (aged 63–90 years) under long term corticosteroid treatment were studied (Table 1). Continuous spinal anaesthesia was selected as the most appropriate anaesthetic procedure, a decision which was not influenced by the investigation. All patients gave informed consent to the study which was approved by the local Committee on Human Research.

Anaesthesia

Anaesthesia was carried out by the same investigator in all patients according to a standard method (Moore, 1965). Although anaesthesia was discontinued at the end of the surgical procedure, the subarachnoid catheter was kept in place for a total of 6 h.

Administration of prednisolone and sampling of biological fluids

The patients (Table 1) were assigned randomly to receive either prednisolone disodium phosphate (Codelsol®; Merck, Sharp & Dohme, West Point,

Table 1 Patient details

Patient's number	*Age (years)*	*Surgery*	*Concomitant diseases*	*Prodrug administered*	*Plasma AUC* ($\mu g\,ml^{-1}\,min$)	*Plasma AUCu* ($\mu g\,ml^{-1}\,min$)	*CSF AUC* ($\mu g\,ml^{-1}\,min$)
1	63	THR	RA	phosphate	216.1	65.1	13.2
2	67	THR	Asthma	phosphate	179.0	50.0	15.8
3	72	TNR	RA	phosphate	266.4	79.6	20.1
4	81	FOS	RA	phosphate	239.0	91.8	18.4
5	78	THR	RA	phosphate	173.1	53.9	20.6
6	78	THR	TA	phthalate	70.3	26.3	3.4
7	77	THR	Asthma	phthalate	96.1	19.5	4.9
8	84	IHR	Prostatic cancer	phthalate	83.1	18.4	2.5
9	90	FOS	RA	phthalate	59.7	11.7	2.5

THR: total hip replacement
TNR: total knee replacement
FOS: femur osteosynthesis
IHR: inguinal hernia repair
RA: rheumatoid arthritis
TA: temporal arteritis

PA) or prednisolone sodium tetrahydrophthalate (Ultracorten-H water soluble®; Ciba-Geigy, Basel, Switzerland). The prodrugs were dosed in equimolar amounts corresponding to 0.8 mg kg^{-1} of prednisolone as an intravenous bolus 10 min after initiation of anaesthesia. Peripheral venous blood and CSF were collected prior to the bolus and 15, 30, 45, 75, 120, 180, 240, 300 and 360 min thereafter from indwelling catheters. The volume of each CSF sample was 1.2 ml.

Analytical methods

Plasma and CSF samples were assayed for prednisolone by h.p.l.c. (Frey *et al.*, 1979). Equilibrium dialysis was carried out on all plasma samples to measure unbound prednisolone concentrations (Frey *et al.*, 1980). The latter were calculated by the method of Behm & Wagner (1979).

Data analysis

AUC values for plasma and CSF were measured using the linear trapezoidal rule. Values beyond the last measured data point were not included in the calculation because the sampling time of 6 h did not allow acceptable extrapolation to infinity in all subjects. Statistical analysis was done using Student's *t*-test with corrections for multiple comparisons.

Results

Maximum concentrations of prednisolone were higher after the administration of the phosphate than the phthalate ester (unbound concentrations, mean ± s.d., 591 ± 135 ng ml^{-1} *vs* 99 ± 68 ng ml^{-1}, $P < 0.0001$) (Figure 1). Maximum plasma concentrations of prednisolone occurred in the 15 min samples after prednisolone phosphate and in the 30 to 120 min samples after prednisolone phthalate ($P < 0.001$) (Figure 1). Values of AUC for total and unbound plasma prednisolone were lower in patients receiving prednisolone phthalate than in patients receiving prednisolone phosphate (AUC 77.3 ± 13.7 *vs* 214.7 ± 35.4 $\mu g\,ml^{-1}$ min, $P < 0.0001$; AUCu, 19.0 ± 5.2 *vs* 68.1 ± 15.7 $\mu g\,ml^{-1}$ min, $P < 0.001$; Table 1). The lowest AUC values were found in patient 9 who was the only patient on concomitant phenytoin treatment (Frey & Frey, 1983). The lower AUCs of prednisolone in plasma after the administration of the phthalate were reflected by lower AUCs of prednisolone in CSF (AUC values in CSF, 3.3 ± 1.0 *vs* 17.6 ± 2.8 $\mu g\,ml^{-1}$ min, $P < 0.001$; Table 1, Figure 1). The concentrations in CSF were correlated linearly with the AUCs of unbound prednisolone in plasma (Table 1; $r = 0.89$, $P < 0.001$).

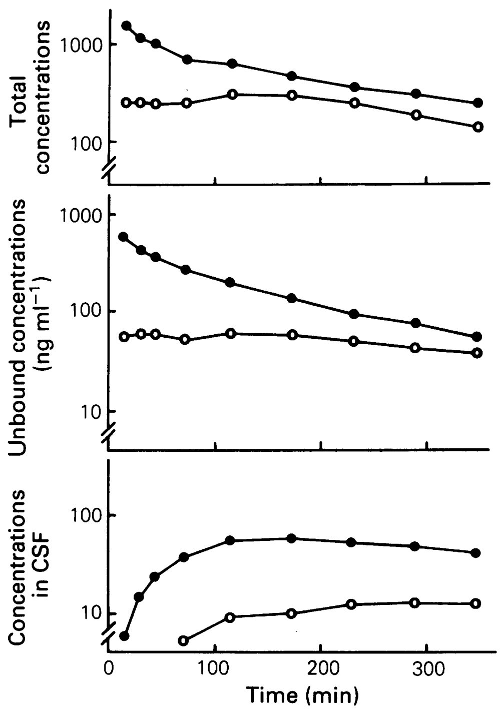

Figure 1 Median concentrations of total plasma prednisolone (upper panel), unbound plasma prednisolone (middle panel) and CSF prednisolone (lower panel) after intravenous doses of prednisolone phosphate (five patients, closed circles) and prednisolone phthalate (four patients, open circles). Doses were equimolor with respect to prednisolone (0.8 mg kg^{-1}).

Higher maximum concentrations of prednisolone were observed in CSF after administration of the phosphate than when the phthalate ester was given ($P < 0.001$). These values ranged from 10 to 37 ng ml^{-1} and from 55 to 85 ng ml^{-1} following prednisolone phthalate and phosphate, respectively.

Discussion

The appearance of prednisolone in plasma following intravenous dosing of the phthalate and phosphate reflects the rate of ester hydrolysis. Previous studies in normal subjects and renal transplant patients showed that the hydrolysis of the phosphate ester is faster than that of the phthalate ester leading to 5–8 times higher total and unbound peak prednisolone concentrations (Frey *et al.*, 1984, 1985). It is likely that the similar differences reported in the present study are pharmacodynamically relevant for the following reasons. First, CSF is in equilibrium with brain extracellular water (Bering, 1974). Thus concentrations of drugs in CSF are likely to reflect those in brain extracellular water. Second, one strategy for drug delivery to the central nervous system is the formation of lipid-soluble prodrugs from water soluble compounds (Bodor & Brewster, 1983; Pardridge, 1988). Thus, provided the transport of prednisolone into the central nervous system is not carrier mediated, prednisolone rather than its higher molecular weight and more water soluble ester-prodrugs would preferentially penetrate the central nervous system. Under these circumstances plasma concentrations of prednisolone would reflect those in brain water. Third, it has been shown that the lower AUCs of unbound prednisolone after administration of prednisolone phthalate compared to those after giving prednisolone phosphate are associated with less immunosuppression (Frey *et al.*, 1984). Thus, therapeutic inequivalence may be expected when patients are treated with equimolar doses of prednisolone phosphate and prednisolone phthalate.

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